9th Annual Diabetes/Heart Disease & Stroke Winter Symposium: Approach to Treatment: The Role of Antidiabetic Therapy- Focus on Oral Medication

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March 12, 2011

Disclosure Verification for:
Name: Kathie L. Hermayer, MD, MS, FACE

The presenter listed above:
___ Does not have any significant financial relationships to disclose

_x_ Has disclosed the following relationship with :

Sanofi Aventis, Eli Lilly, Novo Nordisk

_x_ Research Grants _x_ Speaker's Bureau __ Ownership
__ Consultant for fee __Stock/Bond Holding __ Employment
__Partnership Other:_____

Was this activity Supported by an educational grant or received in-kind support?

_x_Yes Name: CME activity for SC DHEC
__No

Learning Objectives

- Discuss the role of mono therapy and combination therapy and when it should be initiated based on A1C goals.
- Outline the clinical considerations in the selection of pharmacotherapy for type 2 diabetes, including degree of A1C lowering needed, patient specific concerns, adverse effects, co-morbidities, and contraindications.
- Understand the implications of recent clinical trials and meta-analyses on clinical practice decisions.

HbA1C Stratification

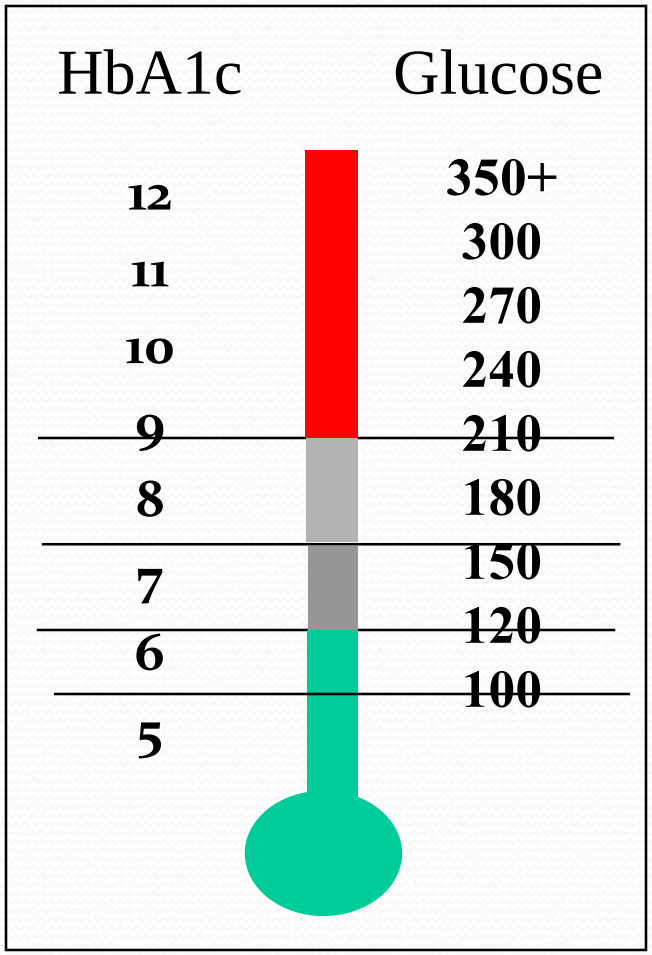
(Hemoglobin A1c : indicates average blood glucose levels over preceding 3 months)

Triple Rx +/- Insulin

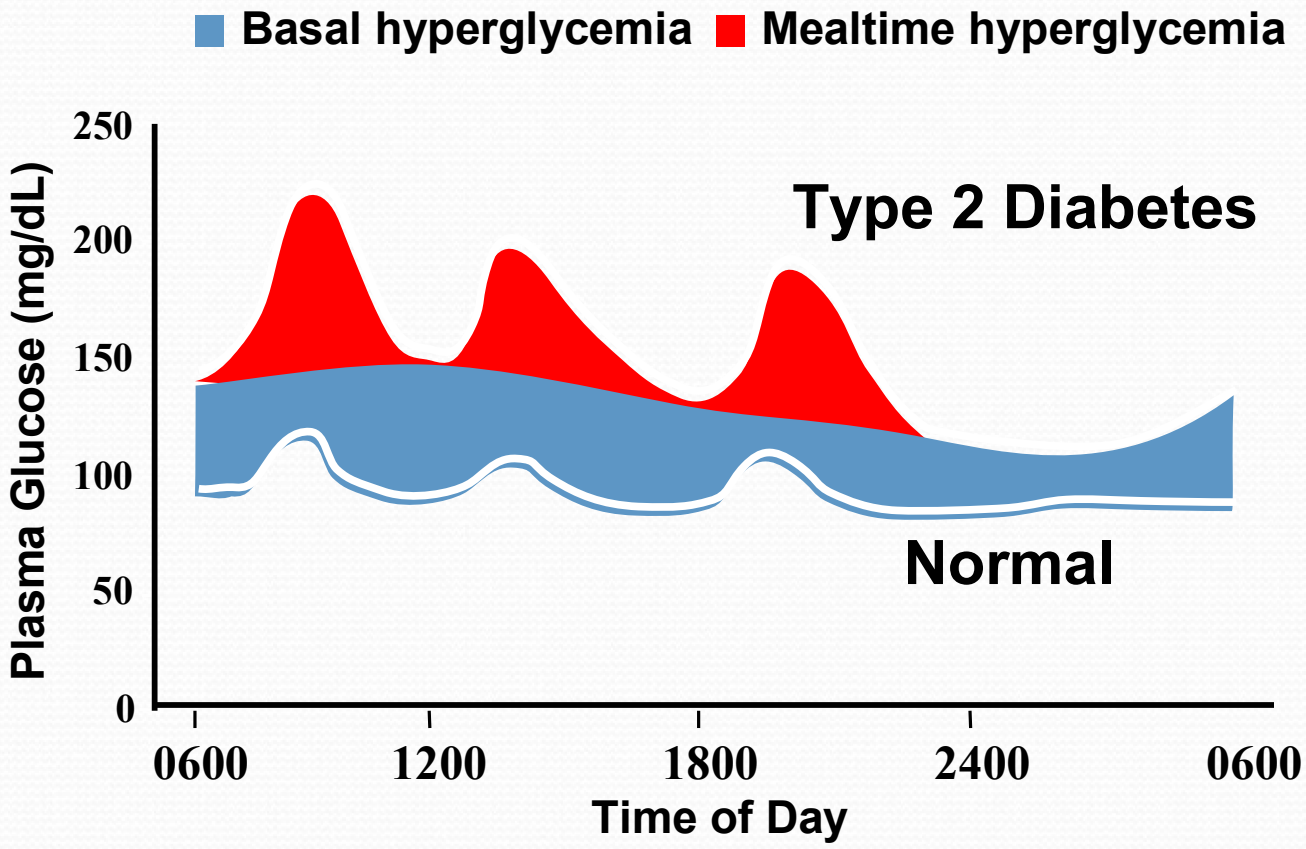
Combination Rx

Monotherapy

Diet and Exercise

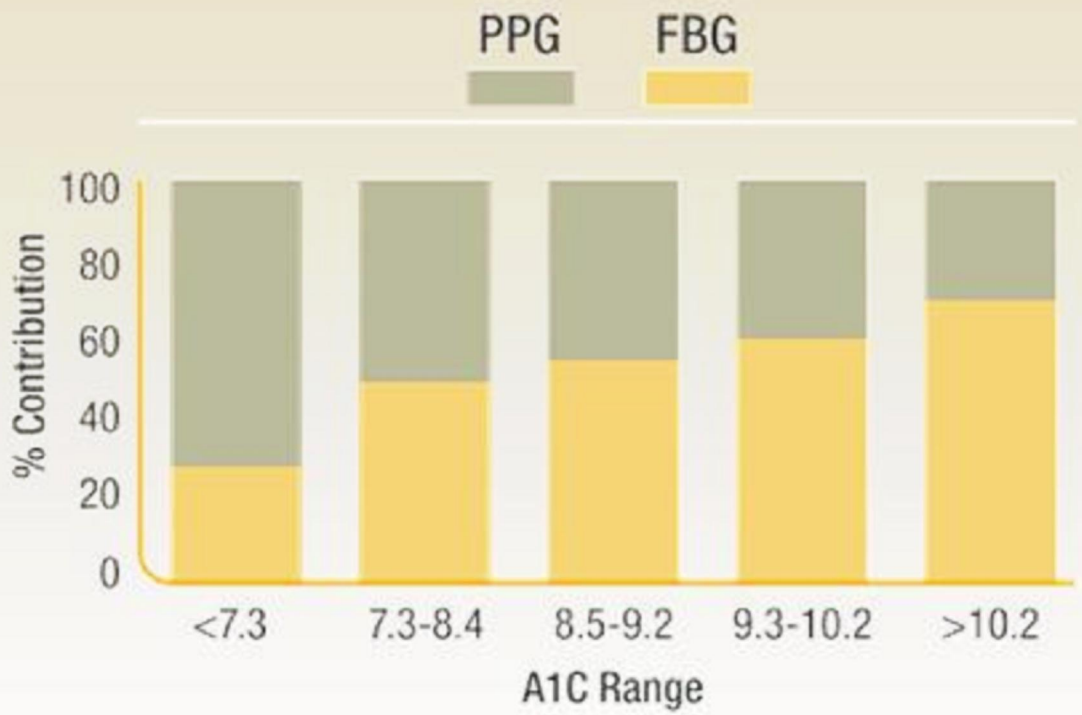


HbA1C = Fasting (Basal) and PPG



Riddle. *Diabetes Care.* 1990;13:676-686.

A1C is a Combination of Both Fasting and Mealtime Glucose

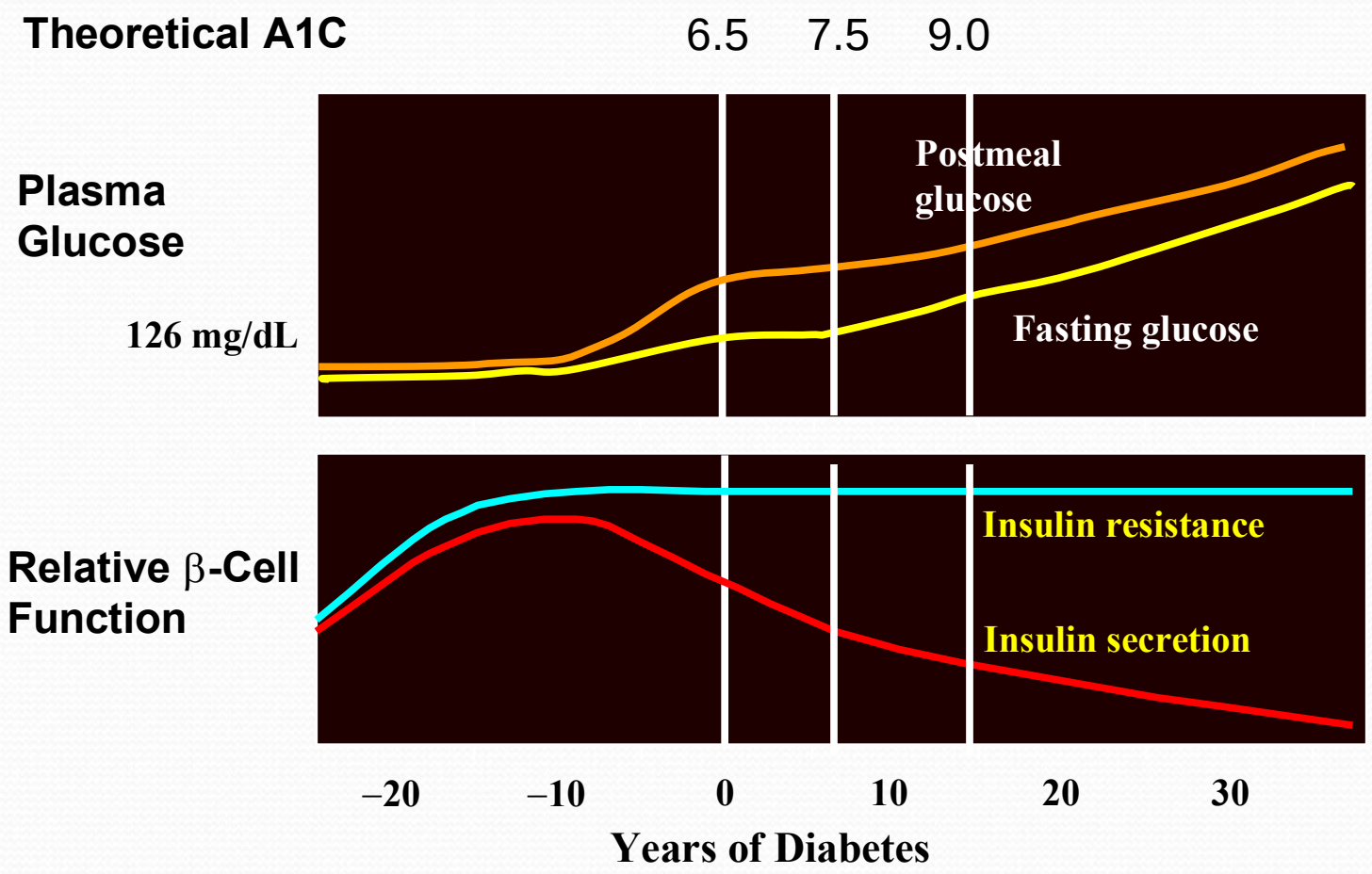


At A1Cs of 7.3 to 9.2, overall glycemia is impacted similarly by fasting blood glucose (FBG) and mealtime glucose

The relative contribution of FBG and PPG blood glucose varies with A1C range.

Monnier L, et al. *Diabetes Care*. 2003;26(3):881-885.

Natural History of Type 2 Diabetes



Adapted from International Diabetes Center (IDC). Minneapolis, Minnesota.

AACE/ACE Consensus Statement

Consensus Panel on Type 2 Diabetes Mellitus:

An Algorithm for Glycemic Control

Helena W. Rodbard, MD, FACP, MACE; Paul S. Jellinger, MD, MACE; Jaime A. Davidson, MD, FACP, MACE; Daniel Einhorn, MD, FACP, FACE; Alan J. Garber, MD, PhD, FACE; George Grunberger, MD, FACP, FACE; Yehuda Handelsman, MD, FACP, FACE; Edward S. Horton, MD, FACE; Harold Lebovitz, MD, FACE; Philip Levy, MD, MACE; Etie S. Moghissi, MD, FACP, FACE; Stanley S. Schwartz, MD, FACE

Statement by American Association of Clinical Endocrinologists and American College of Endocrinology

AACE/ACE Consensus Statement

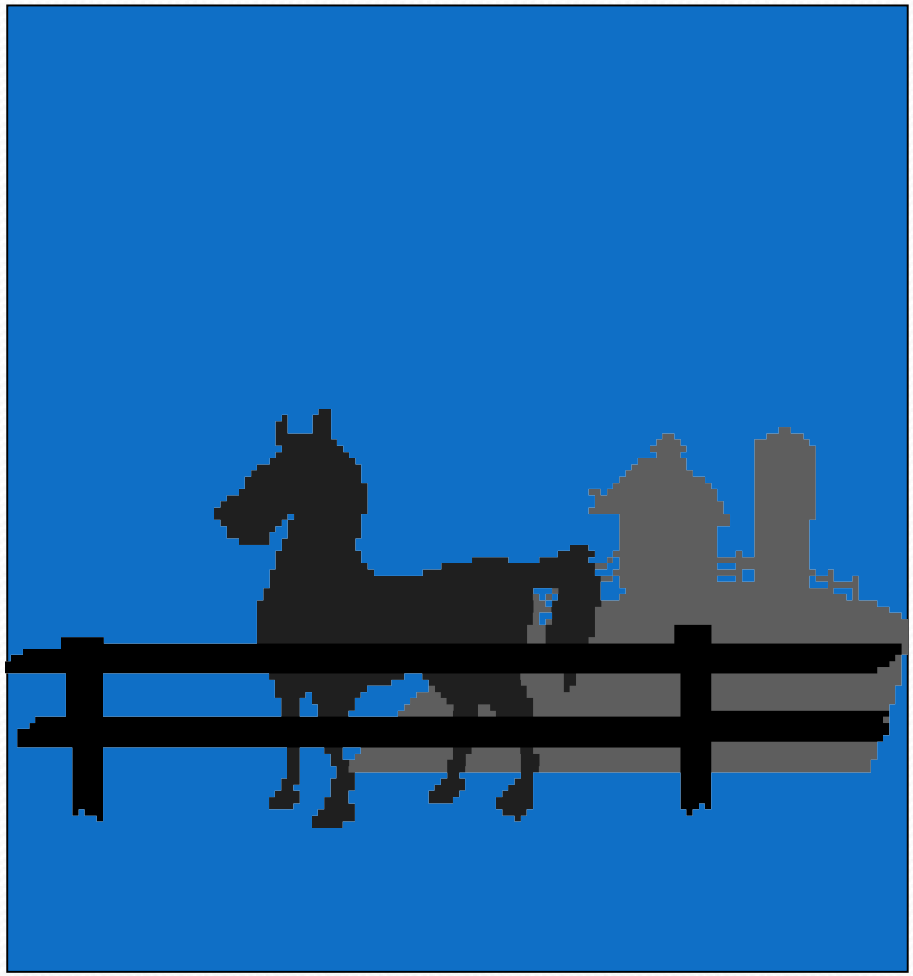
- How Long Should We Give Diet and Exercise i.e. TLC's to Work?
- What Effect Can We Reasonably Expect?
- Does It Matter More Depending on the Stage of the Disease-i.e. Diabetes Prevention vs. Diabetes Treatment?

Effect of Diet and Exercise

	Base-line	Post-Inter-vention	Change
HbA1C (%)	8.31	7.55	-0.76 % (P<0.008)
Body Mass (kg)	83.02	82.48	-0.54 kg (P=.76)

JAMA 2001 Sep 12;286(10):1218-27

Is the Horse Out of the Barn?



We need to distinguish Diabetes *Prevention* from Diabetes *Treatment*

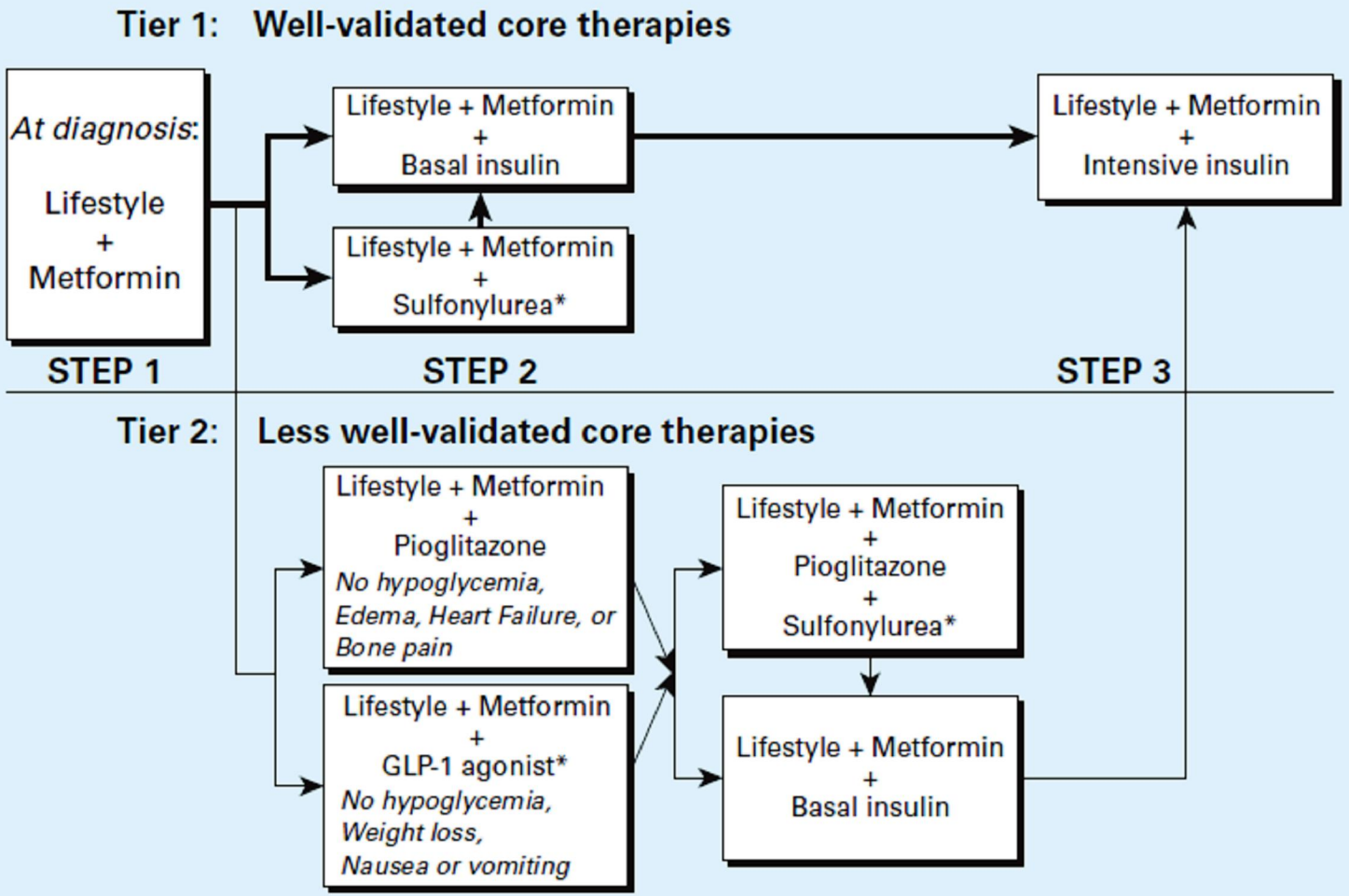
ADA and ACE Glycemic Goals

		ADA 2011	AACE/ACE
Biochemical Index	**Normal**	**Goal**	**Target**
Fasting/preprandial plasma glucose (mg/dL)	<100	70ï 130	≤110
Postprandial plasma glucose (mg/dL)	<140	<180	≤140
Hemoglobin A_{1c} (%)	<6	<7	≤6.5

American Diabetes Association. *Diabetes Care*. 2011;34 Suppl 1

2009 ADA Algorithm for Metabolic Management of T2DM

Algorithm for the metabolic management of T2DM



Source: Nathan DM, Buse JB, Davidson MB, et al. *Diabetes Care*. 2009;32:193-203.[8] Reprinted with permission from the American Diabetes Association.

Principles of AACE/ACE Diabetes Algorithm for Glycemic Control

1. Minimize risk of hypoglycemia
2. Minimize risk of weight gain
3. Consider both fasting and postprandial glucose levels
4. Consider total cost of therapy, not just acquisition cost of the drug
    1. Hypoglycemic events
    2. Drug-related adverse events
    3. Treatment of complicaitons from non-adherence
    4. Additional laboratory tests
5. Begin with metformin which alone usually is not sufficient, so combination therapy usually indicated. Include all major classes of FDA-approved glycemic medications
6. Select therapy stratified by A1C level
7. Select therapy by A1C lowering potential

AACE 2009

AACE/ACE Diabetes Algorithm *For Glycemic Control*

A1C Goal ≤ 6.5%*

LIFESTYLE MODIFICATION

A1C 6.5 – 7.5%**

Monotherapy

MET †	DPP4 [1]	GLP-1	TZD [2]	AGI [3]

↓ *2 - 3 Mos.****

Dual Therapy

		GLP-1 or DPP4 [1]
MET	+	TZD [2]
		Glinide or SU [5]
TZD	+	GLP-1 or DPP4 [1]
MET	+	Colesevelam
		AGI [3]

↓ *2 - 3 Mos.****

Triple Therapy

MET + GLP-1 or DPP4 [1]	+	TZD [2]
		Glinide or SU [4,7]

↓

INSULIN ± Other Agent(s) [6]

A1C 7.6 – 9.0%

Dual Therapy [8]

MET	+	GLP-1 or DPP4 [1] or TZD [2]
		SU or Glinide [4,5]

↓ *2 - 3 Mos.****

Triple Therapy [9]

MET	+	GLP-1 or DPP4 [1]	+ TZD [2]
		GLP-1 or DPP4 [1]	+ SU [7]
		TZD [2]	

↓ *2 - 3 Mos.****

INSULIN ± Other Agent(s) [6]

A1C > 9.0%

Drug Naive | *Under Treatment*

Symptoms | *No Symptoms*

INSULIN ± Other Agent(s) [6]

MET	+	GLP-1 or DPP4 [1]	± SU [7]
		TZD [2]	
		GLP-1 or DPP4 [1]	± TZD [2]

INSULIN ± Other Agent(s) [6]

AACE/ACE Algorithm for Glycemic Control Committee

Cochairpersons:
Helena W. Rodbard, MD, FACP, MACE
Paul S. Jellinger, MD, MACE

Zachary T. Bloomgarden, MD, FACE
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Etie S. Moghissi, MD, FACP, FACE
Stanley S. Schwartz, MD, FACE

* May not be appropriate for all patients

** For patients with diabetes and A1C < 6.5%, pharmacologic Rx may be considered

*** If A1C goal not achieved safely

† Preferred initial agent

1 DPP4 if ↑ PPG and ↑ FPG or GLP-1 if ↑↑ PPG

2 TZD if metabolic syndrome and/or nonalcoholic fatty liver disease (NAFLD)

3 AGI if ↑ PPG

4 Glinide if ↑ PPG or SU if ↑ FPG

5 Low-dose secretagogue recommended

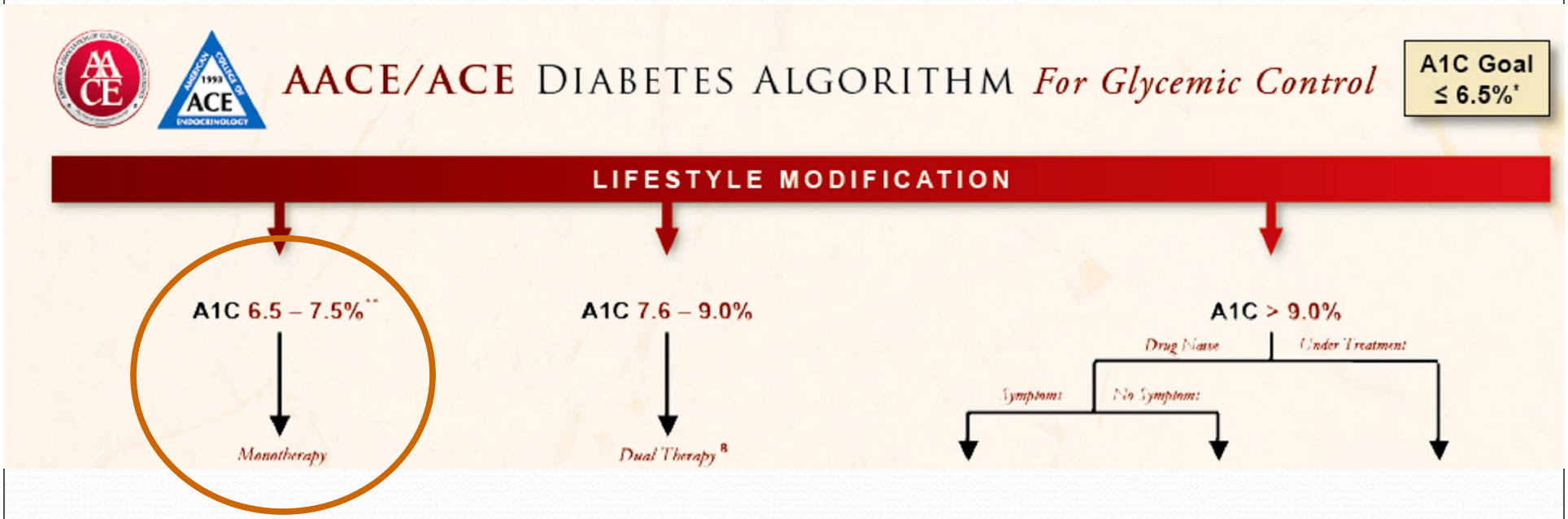
6 a) Discontinue insulin secretagogue with multidose insulin
b) Can use pramlintide with prandial insulin

7 Decrease secretagogue by 50% when added to GLP-1 or DPP-4

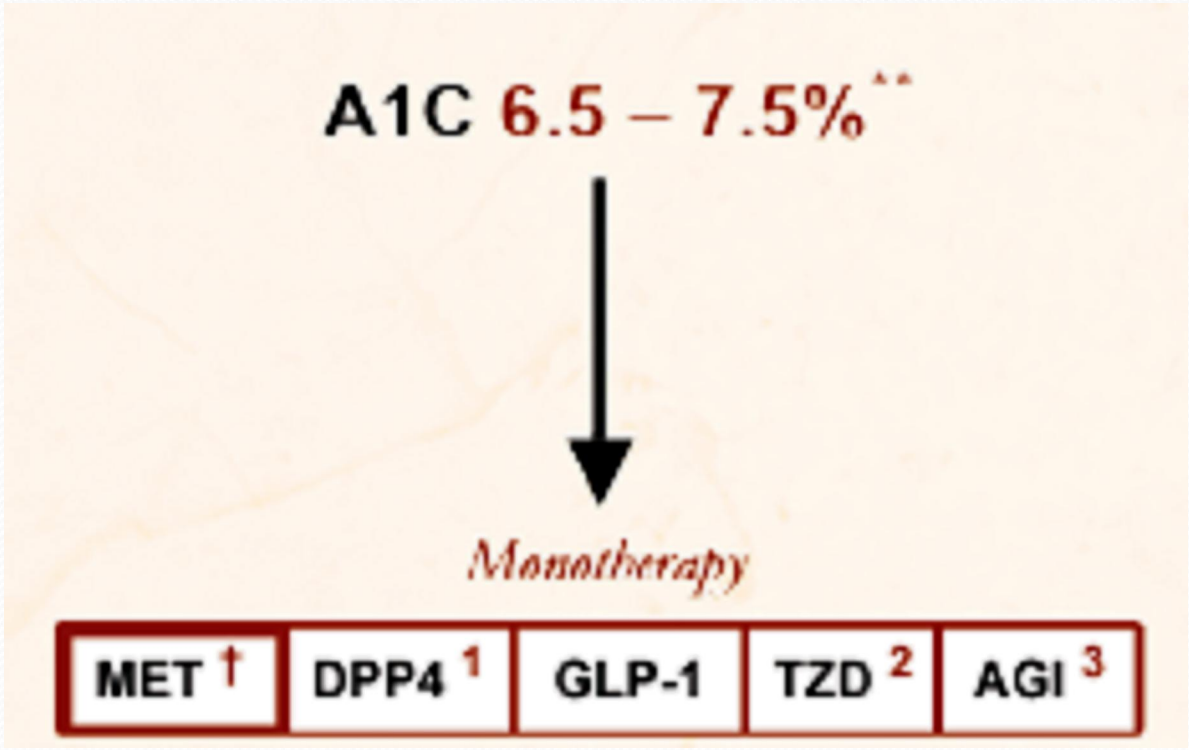
8 If A1C < 8.5%, combination Rx with agents that cause hypoglycemia should be used with caution

9 If A1C > 8.5%, in patients on Dual Therapy, insulin should be considered

Available at **www.aace.com/pub**


AACE/ACE DIABETES ALGORITHM For Glycemic Control
A1C Goal ≤ 6.5%†
LIFESTYLE MODIFICATION
A1C 6.5 – 7.5%††
Monotherapy
A1C 7.6 – 9.0%
Dual Therapy‡
A1C > 9.0%
Drug Naive
Under Treatment
Symptoms
No Symptoms

A1C 6.5-7.5%; Metformin is preferred initial agent (if no contraindications)



**For patients with DM and A1C < 6.5%, pharmacologic Rx may be considered

1 DPP-4 if ↑ PPG and ↑ FPG or GLP-1 if ↑ ↑ PPG

2 TZD if metabolic syndrome and/or NAFLD

3 AGI if ↑ PPG

A1C 6.5-7.5%; *if Mono Rx failure*

Dual Therapy

MET	+	GLP-1 or DPP4 [1]
		TZD [2]
		Glinide or SU [5]
TZD	+	GLP-1 or DPP4 [1]
MET	+	Colesevelam
		AGI [3]

1 DPP-4 if ↑ PPG and ↑ FPG or GLP-1 if ↑ ↑ PPG
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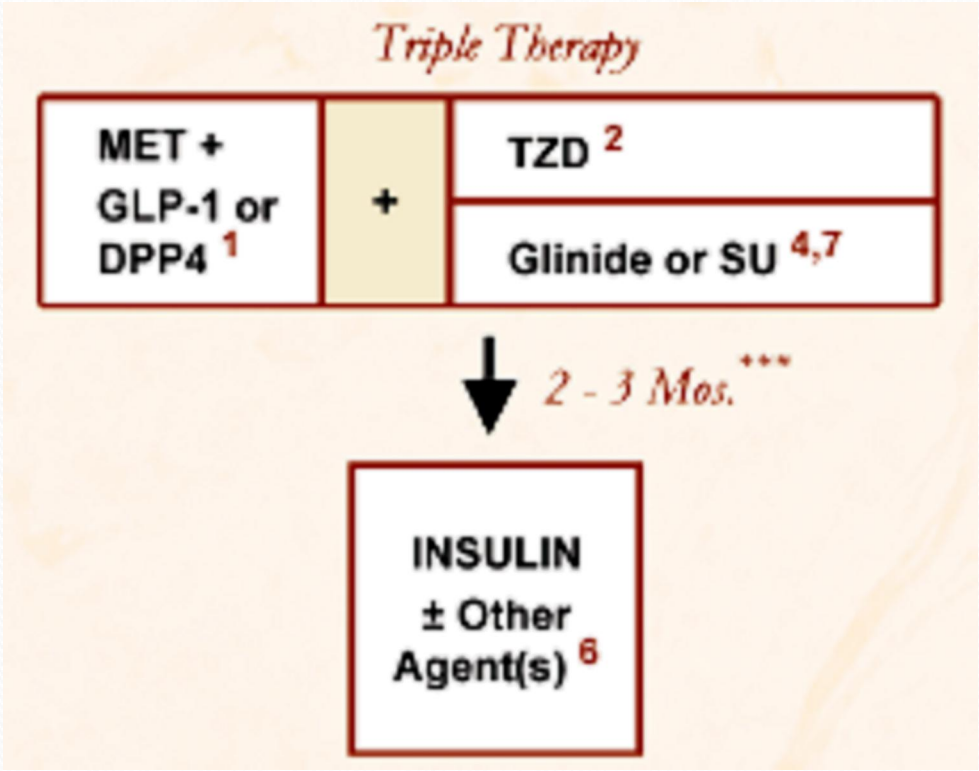
4 Glinide if ↑ PPG or SU if ↑ FPG
5 Low-dose secretagogue recommended

A1C 6.5-7.5%; *if Dual Rx failure*



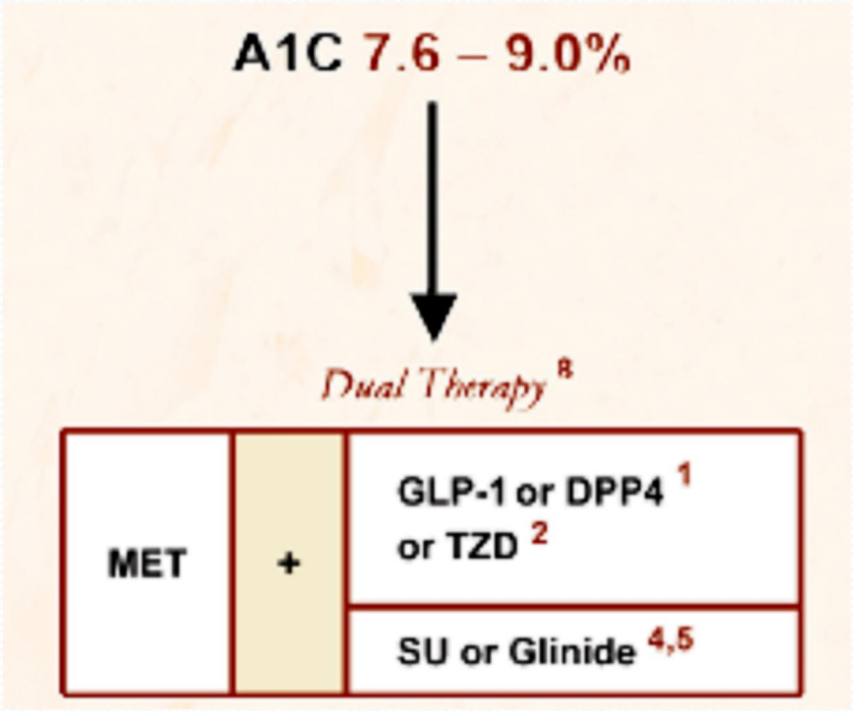
2 TZD if metabolic syndrome and/or NAFLD

4 Glinide if ↑ PPG or SU if ↑ FPG

6 a) Discontinue insulin secretagogue with multi-dose insulin
b) Can use pramlinitide with prandial insulin

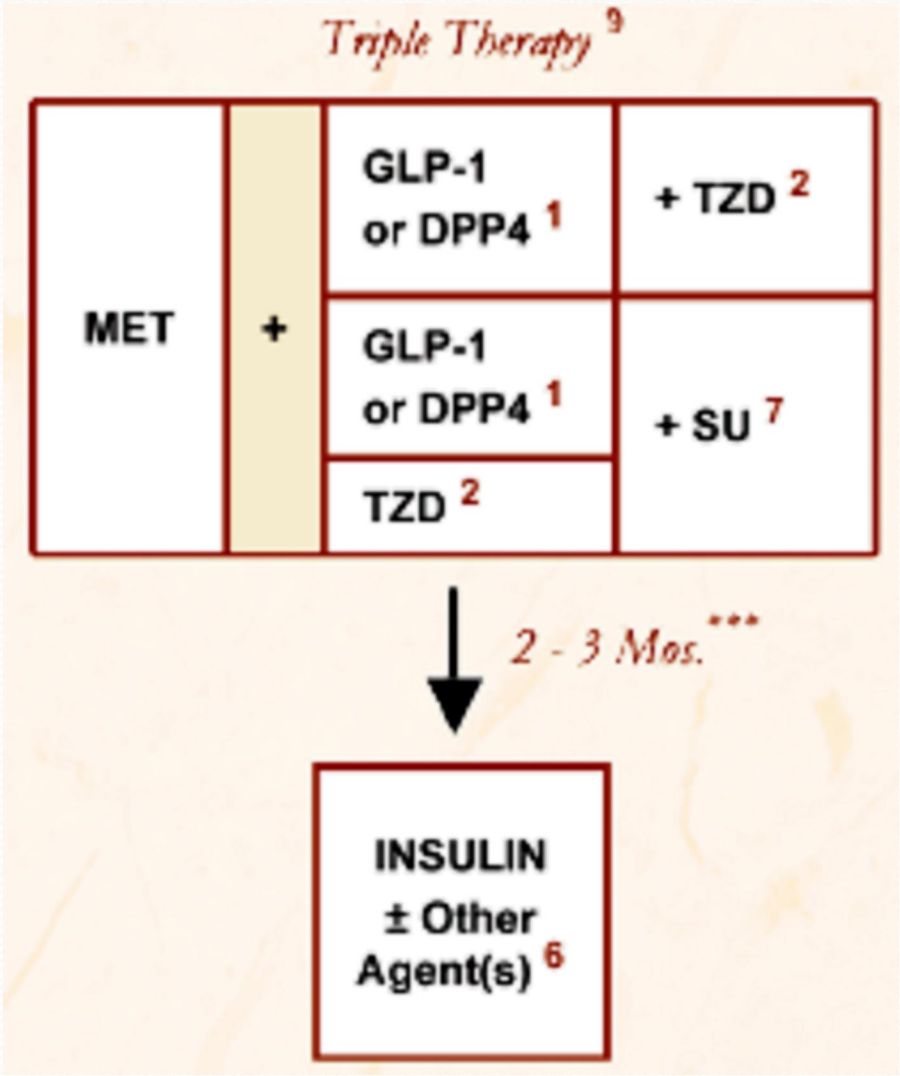
7 Decrease secretagogue by 50% when added to GLP-1 or DPP-4

A1C 7.6-9.0%-Metformin is still preferred initial agent (if no contraindications)



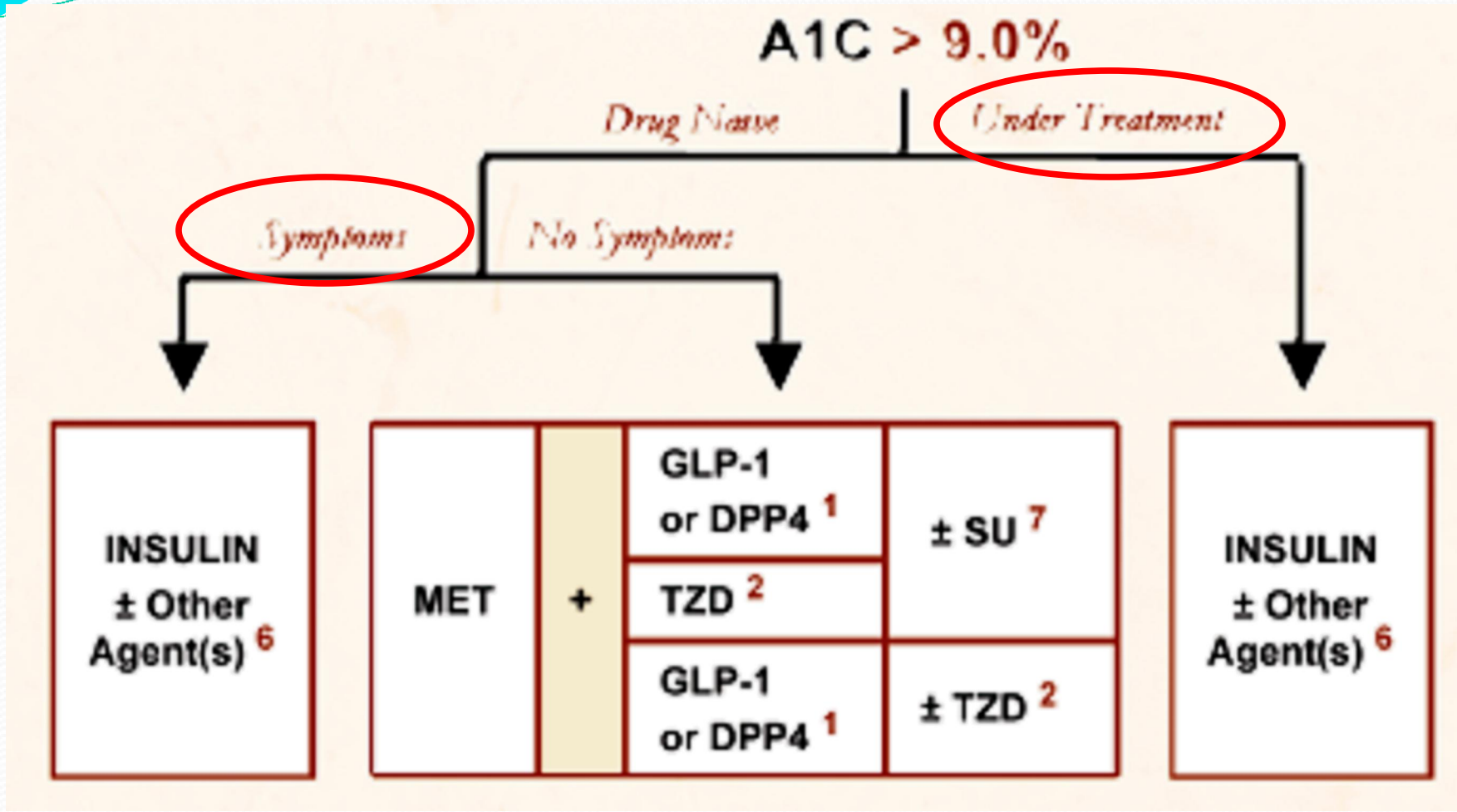
1 DPP-4 if ↑ PPG and ↑ FPG or GLP-1 if ↑ ↑ PPG
2 TZD if metabolic syndrome and/or NAFLD
4 Glinide if ↑ PPG or SU if ↑ FPG
5 Low-dose secretagogue recommended
8 If HbA1C < 8.5%, combination Rx with agents that cause hypoglycemia should be used with caution

A1C 7.6-9.0%; *If A1C Goal not achieved safely*



9 If HbA1C > 8.5% in patients on dual therapy, insulin should be considered

A1C > 9.0%



6 a) Discontinue insulin secretagogue with multi-dose insulin
b) Can use pramlinitide with prandial insulin

7 Decrease secretagogue by 50% when added to GLP-1 or DPP-4

Objectives

- ✓ Discuss the role of mono therapy and combination therapy and when it should be initiated based on A1C goals.
- ❑ Outline the clinical considerations in the selection of pharmacotherapy for type 2 diabetes, including degree of A1C lowering needed, patient specific concerns, adverse effects, co-morbidities, and contraindications.
- ❑ Understand the implications of recent clinical trials and meta-analyses on clinical practice decisions.

Oral Agents for Treatment of Type 2 Diabetes

- Biguanides
  - Metformin
- Secretagogues
  - Sulfonylureas: Glipizide, Glyburide, Glimepiride
  - Glinides: Nateglinide, Repaglinide
- Thiazolidinediones
  - Pioglitazone, Rosiglitazone
- Alpha Glucosidase Inhibitors
  - Acarbose, Miglitol
- DPP-4 Inhibitors
  - Sitagliptin, Saxagliptin
- GLP-1 and Amylin analogues
  - Exenatide, Pramlinitide
- Bile Acid Sequestrants
  - Colesevelam

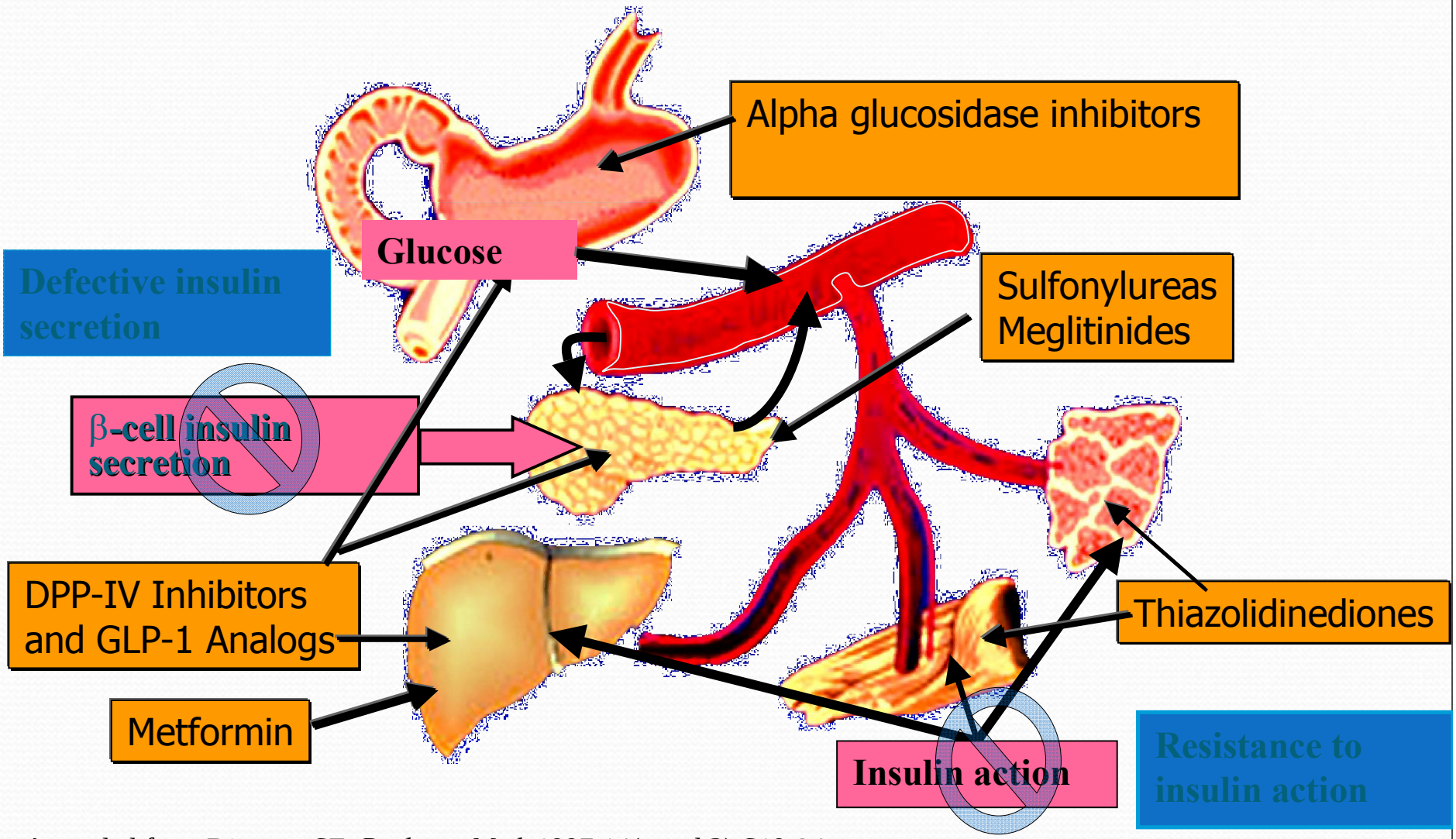
AACE Diabetes Clinical Practice Guidelines

Table 4.6. Effect of Oral Therapies on Hemoglobin A_{1c} Levels in Patients With Diabetes Mellitus

Drug Therapy	Hemoglobin A_{1c} Reduction, %
Monotherapy	
Sulfonylureas	0.9 to 2.5 (10,54)
Biguanide (metformin)	1.1 to 3.0 (16,55-58)
Thiazolidinediones	1.5 to 1.6 (7,8,59)
α-Glucosidase inhibitors	0.6 to 1.3 (57,14,60)
Dipeptidyl-peptidase 4 inhibitors	0.8 (23)
Noninsulin Injectables	
Pramlintide	0.43 to 0.56 (39)
Exenatide	0.8 to 0.9 (40)
Combination Therapy	
Sulfonylurea + metformin	1.7 (16)
Sulfonylurea + rosiglitazone	1.4 (18)
Sulfonylurea + pioglitazone	1.2 (19)
Sulfonylurea + acarbose	1.3 (20)
Repaglinide + metformin	1.4 (17)
Pioglitazone + metformin	0.7 (21)
Rosiglitazone + metformin	0.8 (22)
Dipeptidyl-peptidase 4 inhibitor + metformin	0.7 (23)
Dipeptidyl-peptidase 4 inhibitor + pioglitazone	0.7 (23)

AACE Diabetes Mellitus Guidelines, Endocrine Practice; 13(Suppl 1) 2007: 27.

Overview of Glucose Regulation



Amended from Dinneen SF. *Diabetes Med*. 1997;14(suppl 3):S19-24.

T2DM: Therapeutic Landscape, 2010

Agent	Examples	Mechanism	Action
SUs	Glyburide, Glipizide, Glimepiride	Closes K_{ATP} channels	↑ Pancreatic insulin secretion
Glinides	Repaglinide, Nateglinide	Closes K_{ATP} channels	↑ Pancreatic insulin secretion
Biguanides	Metformin	Activates AMP-kinase	↓ Hepatic glucose production
TZDs	Rosiglitazone, Pioglitazone	Activates PPAR-γ	↑ Peripheral insulin sensitivity
α-GIs	Acarbose, Miglitol	Blocks SB alpha-glucosidase	↓ Intestinal carbohydrate absorption
GLP-1 agonists	Exenatide Liraglutide	Activates GLP-1 receptors	↑ Pancreatic insulin secretion; ↓ glucagon secretion; delays gastric emptying; ↑ satiety
Amylinomi-metics	Pramlintide	Activates amylin receptors	↓ Pancreatic glucagon secretion; delays gastric emptying; ↑ satiety
DPP-4 inhibitors	Sitagliptin, Saxagliptin	Inhibits DPP-4, ↑ endogenous incretins	↑ Pancreatic insulin secretion; ↓ pancreatic glucagon secretion
Bile acid sequestrants	Colesevelam	Binds bile acid cholesterol	↓ Hepatic glucose production ↑ GLP-1

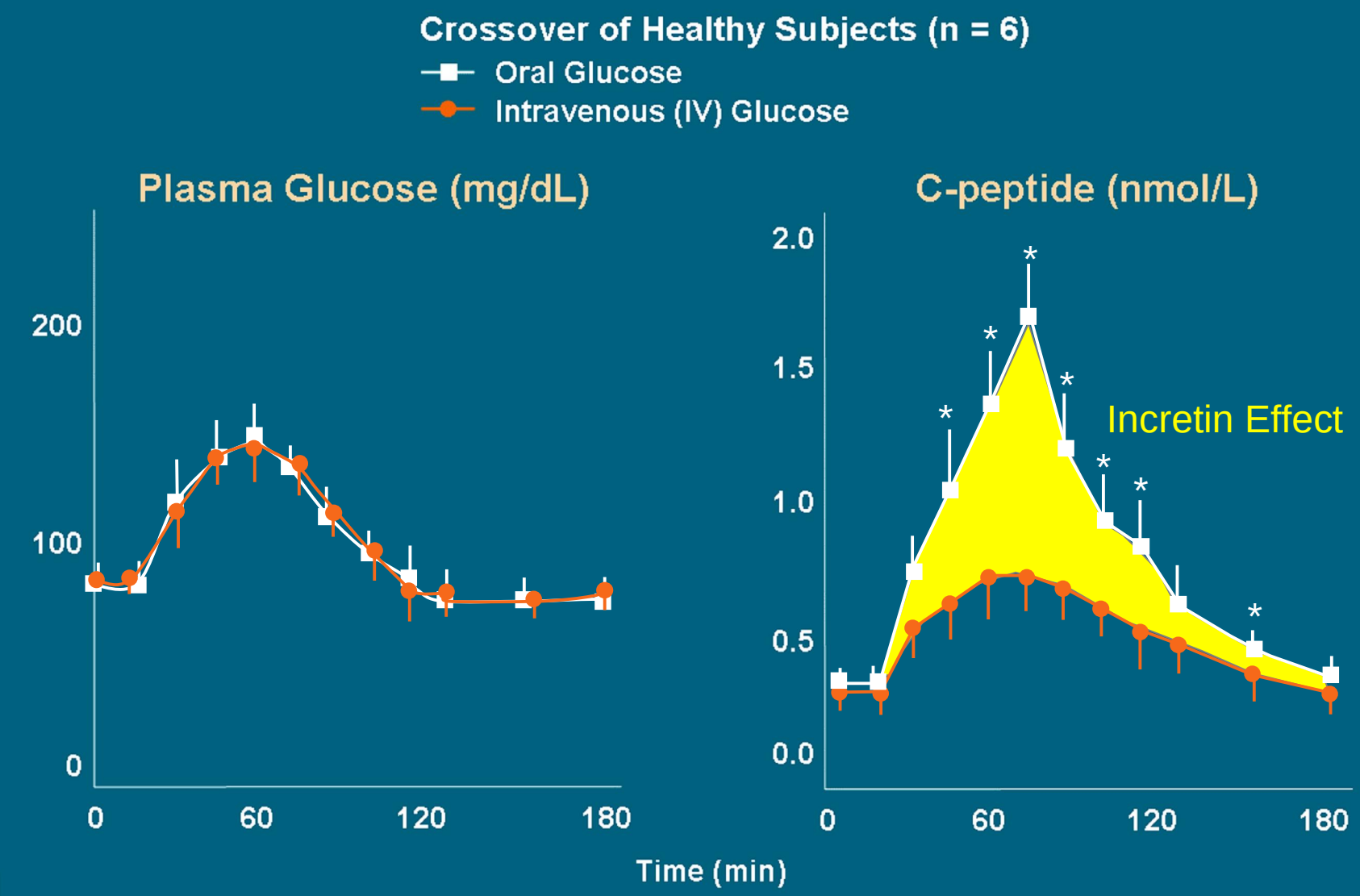
Biguanides

Metformin (*Glucophage®*)

- *Mechanism:* ↓ hepatic glucose production; lowers FPG more than PPG
- *Efficacy:* moderate (↓ HbA1c 1-2%)
- *Advantages:* weight loss; no hypoglycemia, ? CV benefits
- *Disadvantages:* GI side effects (diarrhea), lactic acidosis *(rare)*, contraindications (renal disease and CHF)

The Incretin Effect

Beta-Cell Response to Oral vs IV Glucose

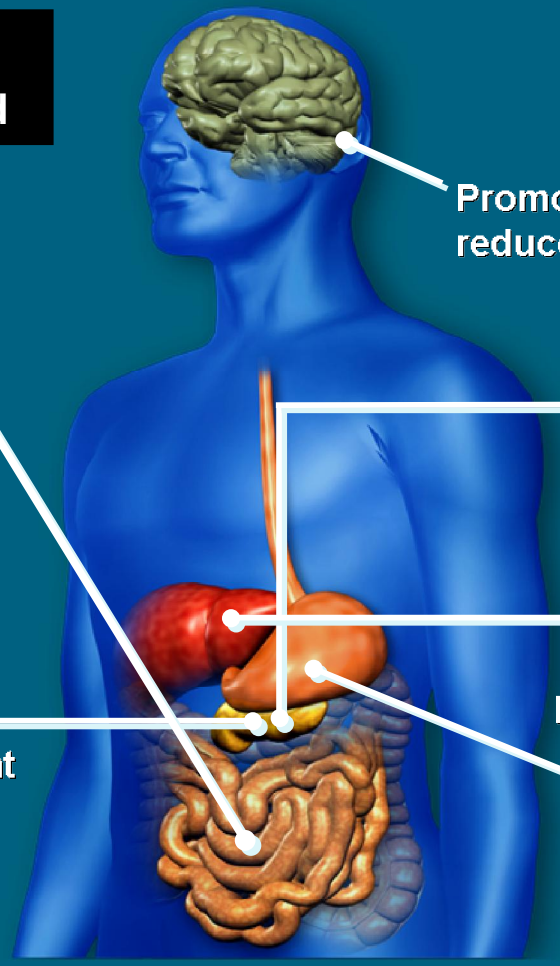


Mean (SE); *$P \leq 0.05$

Data from Nauck MA, et al. *J Clin Endocrinol Metab*. 1986;63:492-498

GLP-1 Effects in Humans

Understanding the Natural Role of Incretins



GLP-1 secreted upon the ingestion of food

↑ Beta-cell response

↓ Beta-cell workload

Promotes satiety and reduces appetite

Alpha cells:
↓ Postprandial glucagon secretion

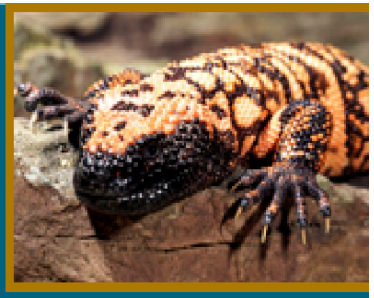
Liver:
↓ Glucagon reduces hepatic glucose output

Beta cells:
Enhances glucose-dependent insulin secretion

Stomach:
Helps regulate gastric emptying

Adapted from Flint A, et al. *J Clin Invest*. 1998;101:515-520
Adapted from Larsson H, et al. *Acta Physiol Scand*. 1997;160:413-422
Adapted from Nauck MA, et al. *Diabetologia*. 1996;39:1546-1553
Adapted from Drucker DJ. *Diabetes*. 1998;47:159-169

- Exenatide
  - Synthetic version of salivary protein found in the Gila monster
  - More than 50% overlap with human GLP-1
    - Binds to known human GLP-1 receptors on beta cells (*in vitro*)
    - Resistant to DPP-IV inactivation



Exenatide	**H G E G T F T S D L S K Q M E E E A V R L F I E W L K N G G P S S G A P P P S-NH_2**
GLP-1 Human	**H A E G T F T S D V S S Y L E G Q A A K E F I A W L V K G R-NH_2**

Site of DPP-IV Inactivation

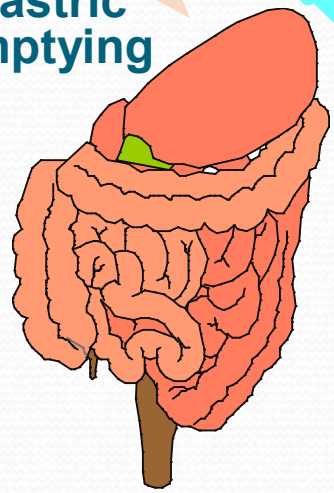
- Following injection, exenatide is measurable in plasma for up to 10 hours

Adapted from Nielsen LL, et al. *Regul Pept.* 2004;117:77-88
Adapted from Kolterman OG, et al. *Am J Health-Syst Pharm.* 2005;62:173-181

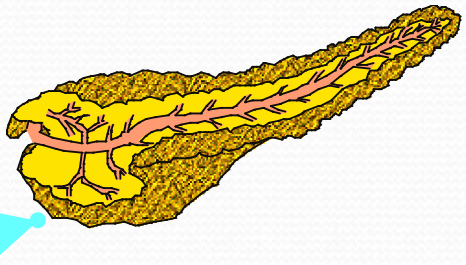
Physiology of the Incretin System

A Key Regulator of Post-Prandial Glucose Metabolism

gastric emptying



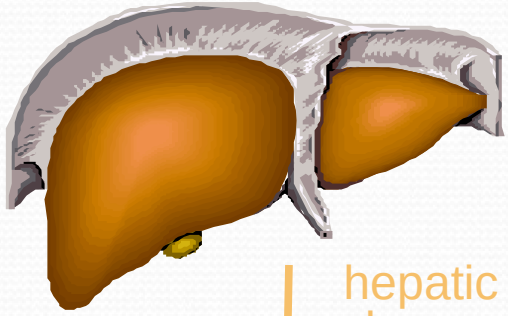
GLP-1
GIP



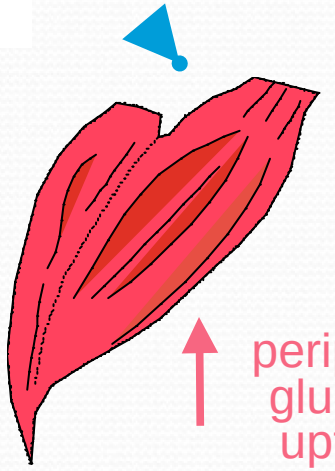
insulin secretion

DPP-4 Inhibitor

glucagon secretion



hepatic glucose production



peripheral glucose uptake

DPP-4 Inhibitors

Sitagliptin (*Januvia*®)

Saxagliptin (*Onglyza*®)

- *Mechanism:* ↑ insulin secretion (BG-dependent), ↓ glucagon secretion
  Lowers PPG more than FPG
- *Efficacy:* modest (↓ HbA1c 0.6-0.8%)
- *Advantages:* weight neutral,
  no hypoglycemia,
  ? β-cell preservation
- *Disadvantages:* cost, ? urticaria

GLP-1 Agonist (Incretin Mimetic)

Exenatide (*Byetta*®)
Liraglutide (*Victoza*®)

- *Mechanism:* ↑ insulin secretion (BG-dependent), ↓ glucagon secretion; satiety; slows gastric emptying
  Moderate to marked PPG lowering
- *Efficacy:* moderate (↓ HbA1c 1%)
- *Advantages:* weight loss, can restore 1st phase insulin secretion, infrequent hypoglycemia,
  ? β-cell preservation
- *Disadvantages:* cost, injection

Sulfonylureas

Glyburide (*Micronase*®, *Diabeta* ®, *Glynase* ®)
Glipizide (*Glucotrol*®), Glimepiride (*Amaryl*®)

- *Mechanism:* ↑ pancreatic insulin secretion
  Lowers both FPG and PPG
- *Efficacy:* moderate (↓ HbA1c 1-2%)
- *Advantages:* inexpensive; reduces microvascular complications
- *Disadvantages:* weight gain, hypoglycemia,

Glinides-(Non-SU Secretagogues)

Repaglinide (*Prandin*®)
Nateglinide (*Starlix*®)

- *Mechanism:* ↑ pancreatic insulin secretion
  Primarily Lowers PPG
- *Efficacy:* moderate (↓ HbA1c 1-1.5%)
- *Advantages:* more physiologic insulin secretion,
  targets post-prandial glucose
- *Disadvantages:* weight gain, hypoglycemia,
  frequent dosing, cost

Thiazolidinediones

Rosiglitazone (*Avandia*®)
Pioglitazone (*Actos*®)

- *Mechanism:* ↓ insulin resistance
- *Efficacy:* moderate (↓ HbA1c 1-1.5%)
  Lowers both FPG and PPG
- *Advantages:* no hypoglycemia, β-cell preservation,
  ? CV benefits (pioglitazone)
- *Disadvantages:* fluid retention / heart failure,
  weight gain, cost, slow onset of action,
  bone fractures

Bile Acid Sequestrants

Colesevelam (*Welchol*®)

- *Mechanism:* Involves Bile Acid receptors
- *Efficacy:* modest (↓ HbA1C @ 0.5%)
- *Advantages:* ↓ LDL-C
  weight neutral,
  no hypoglycemia,
- *Disadvantages:* GI-constipation, ↑ TGs,
  cost

Alpha-Glucosidase Inhibitors

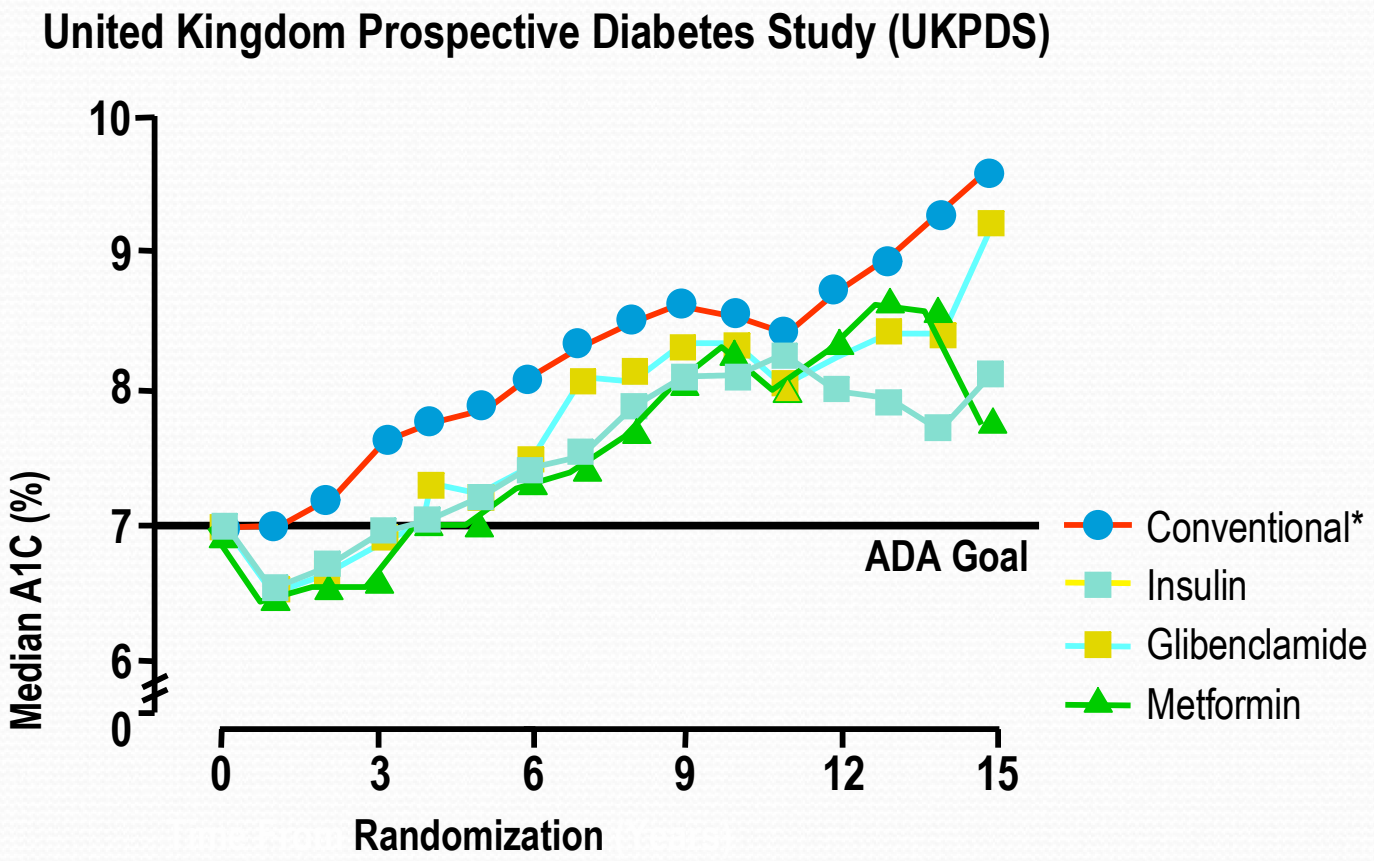
Acarbose (*Precose*®)
Miglitol (*Glyset*®)

- *Mechanism:* ↓ gut carbohydrate absorption
- *Efficacy:* modest (↓ HbA1c 0.5-1.0%)
  PPG lowering
- *Advantages:* weight neutral, non-systemic drug,
  targets post-prandial glucose
- *Disadvantages:* GI side effects (gas)
  frequent dosing, cost

Objectives

- ✓ Discuss the role of mono therapy and combination therapy and when it should be initiated based on A1C goals.
- ✓ Outline the clinical considerations in the selection of pharmacotherapy for type 2 diabetes, including degree of A1C lowering needed, patient specific concerns, adverse effects, co-morbidities, and contraindications.
- ❑ Understand the implications of recent clinical trials and meta-analyses on clinical practice decisions.

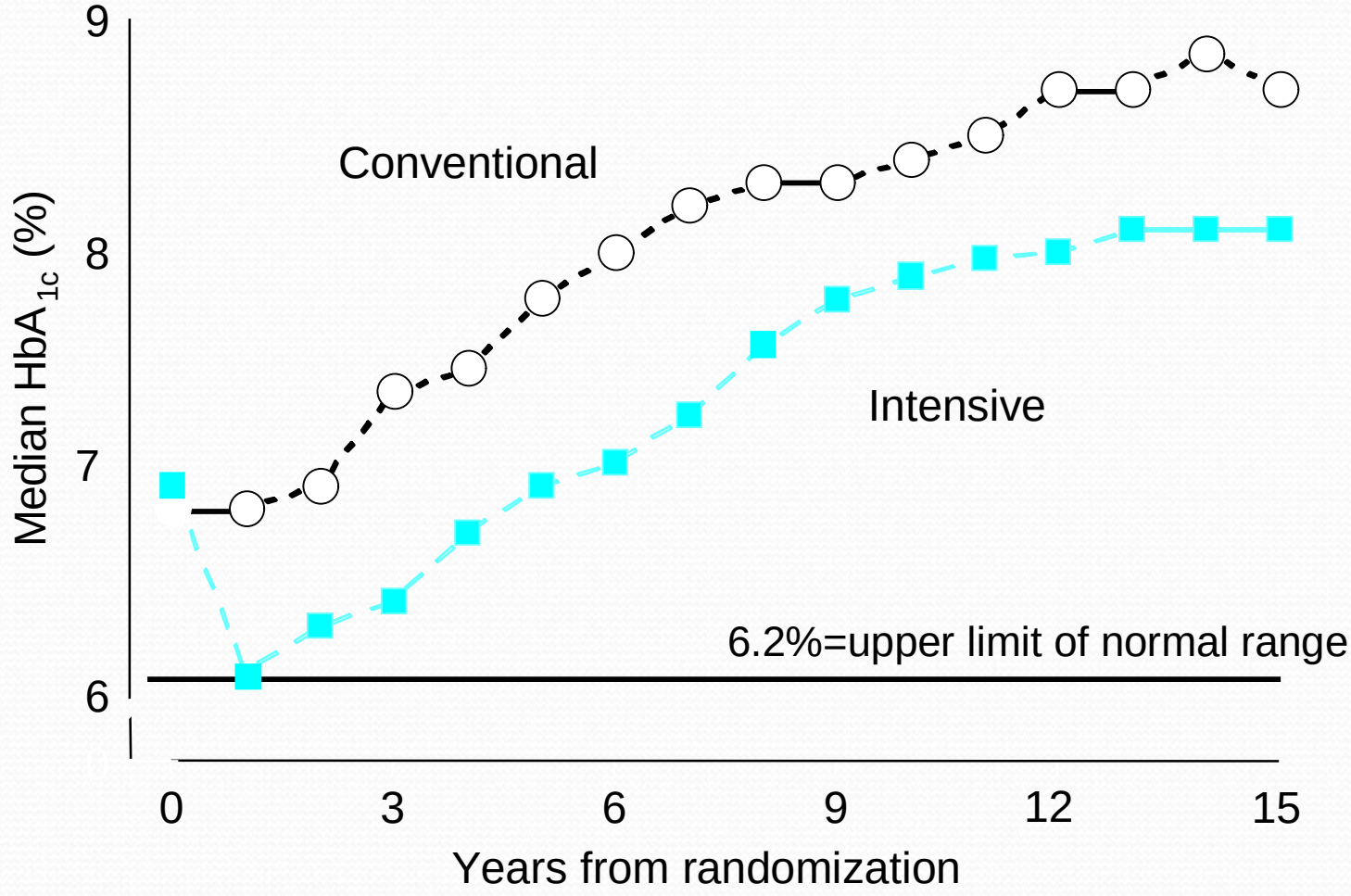
UKPDS: Effects of Treatment on HbA_{1c} in Glucose Control Study



*Conventional therapy defined as dietary advice given at 3-month intervals where FPG was targeted at best levels feasible in clinical practice. If FPG exceeded 270 mg/dL, then patients were re-randomized to receive non-intensive metformin, chlorpropamide, glibenclamide, or insulin. If FPG exceeded 270 mg/dL again, then those on SU would have metformin added. If FPG exceeded 270 mg/dL after this, then insulin was substituted.

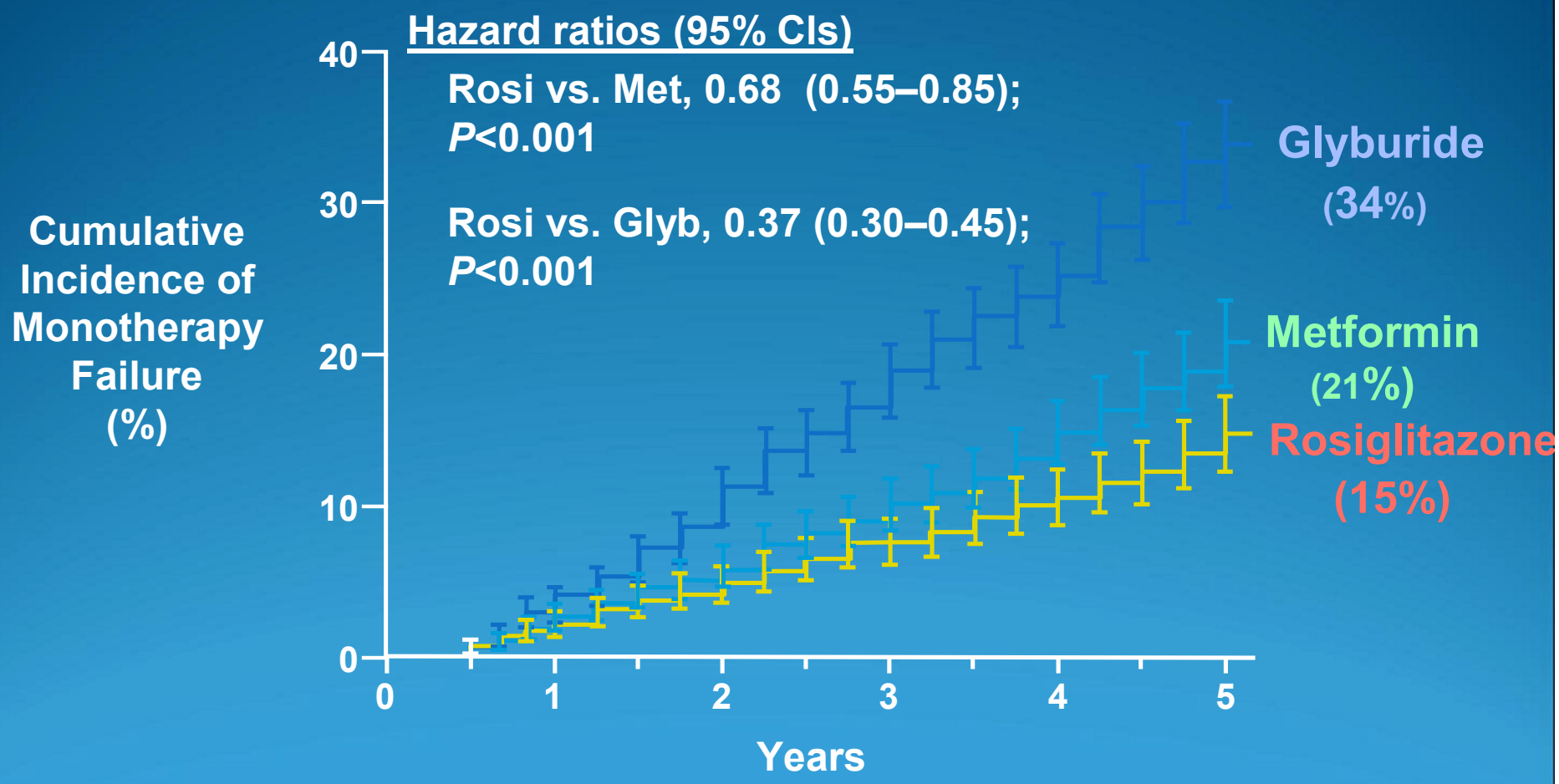
Adapted with permission from UK Prospective Diabetes Study (UKPDS 34) Group. *Lancet*. 1998;352:854-865.

UKPDS: Effects of Treatment on HbA_{1c} in Glucose Control Study



UKPDS Group. *Lancet*. 1998;352:837-853

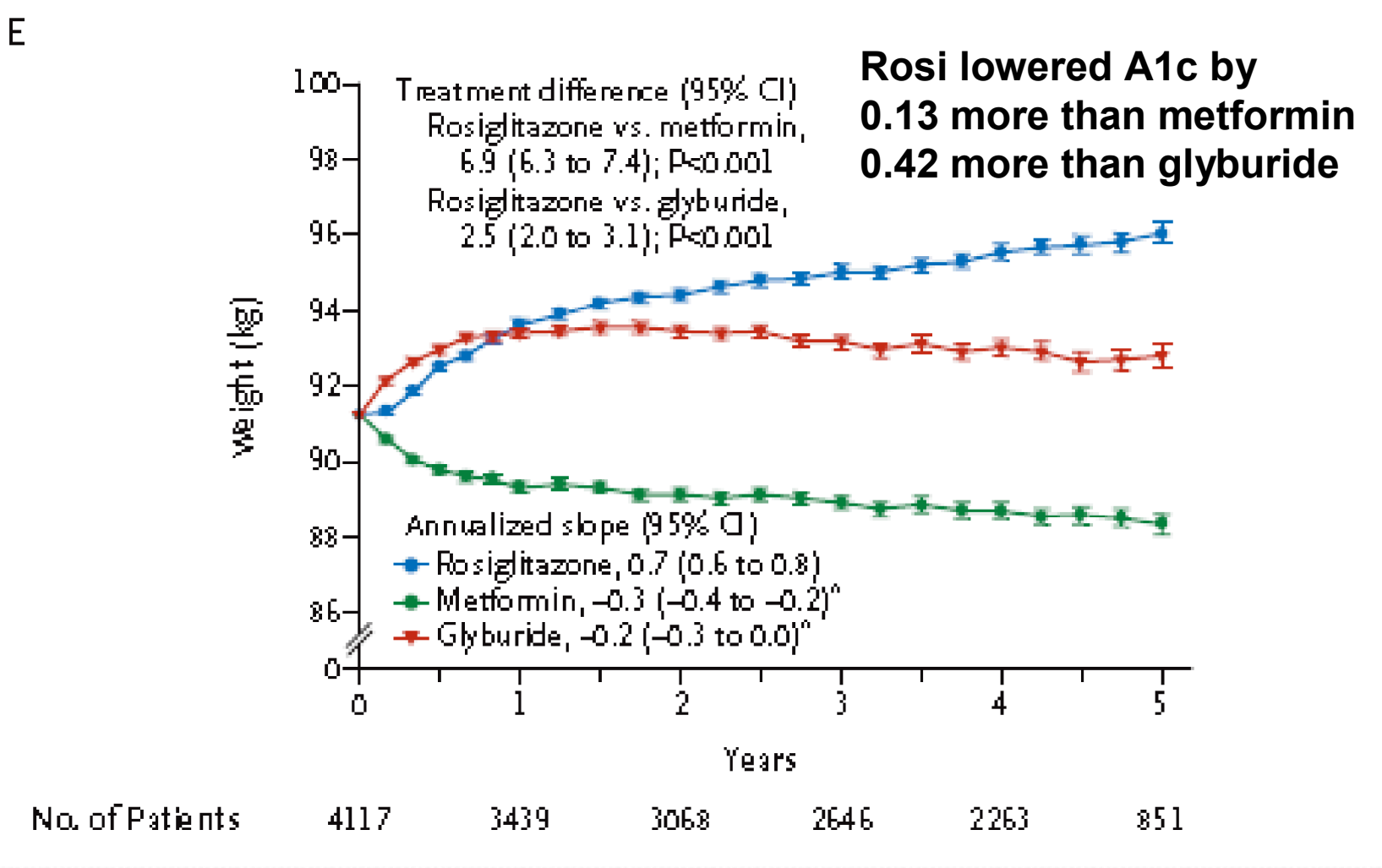
ADOPT: Cumulative Incidence of Monotherapy Failure* at 5 Years



* FPG > 180 mg/dl

Kahn SE et al. *N Engl J Med.* 2006;355:2427-2443.

ADOPT Trial: Rosi Effects on Weight Greater Than Met or SU



N England J Med 2006;355:2427-43

Rosiglitazone & Cardiovascular Risk

Study (N=42)	Rosiglitazone	Control	OR (95% CI)	P
MI				
Small trials			.39)	0.15
DREAM*			.68)	0.22
ADOPT			.21)	0.27
Overall			.98)	**0.03**
CV Death*				
Small trials			.91)	0.02
DREAMÀ			.78)	0.67
ADOPT	2 / 1456 (0.14%)	5 / 2854 (0.18%)	0.80 (0.17-3.86)	0.78
Overall			**1.64 (0.98-2.74)**	**0.06**

RECORD Trial
N=4447
Rosi + Met/SU *vs.* Met + SU
CV Hospitalization or Death (5.5 yrs)
HR=0.99 (0.85 - 1.16)

Home PD, et al. *Lancet.* 2009;373:2125-2135.

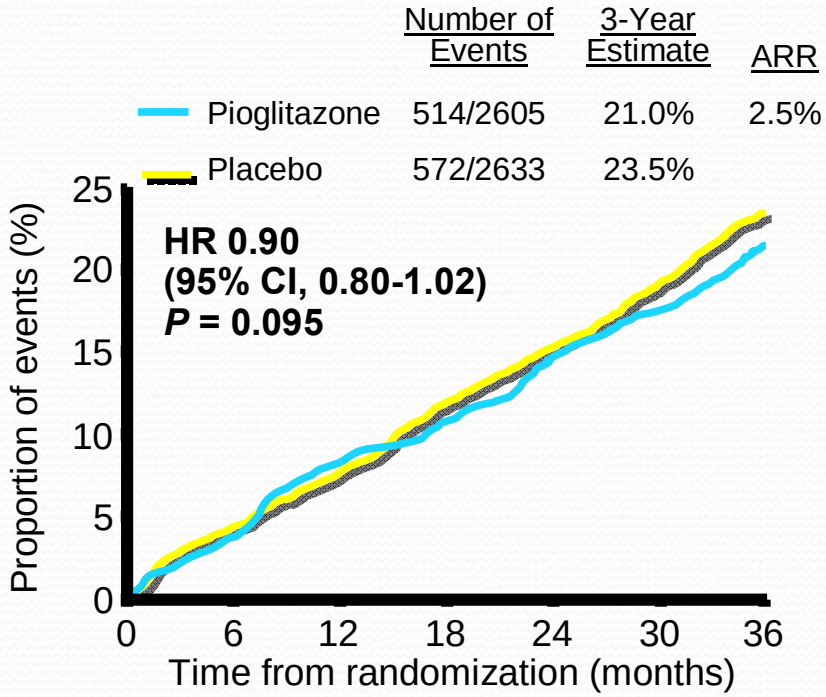
ÀIGT/IFG patients

*all-cause death, OR=1.18 (0.89-1.55, P=0.24)

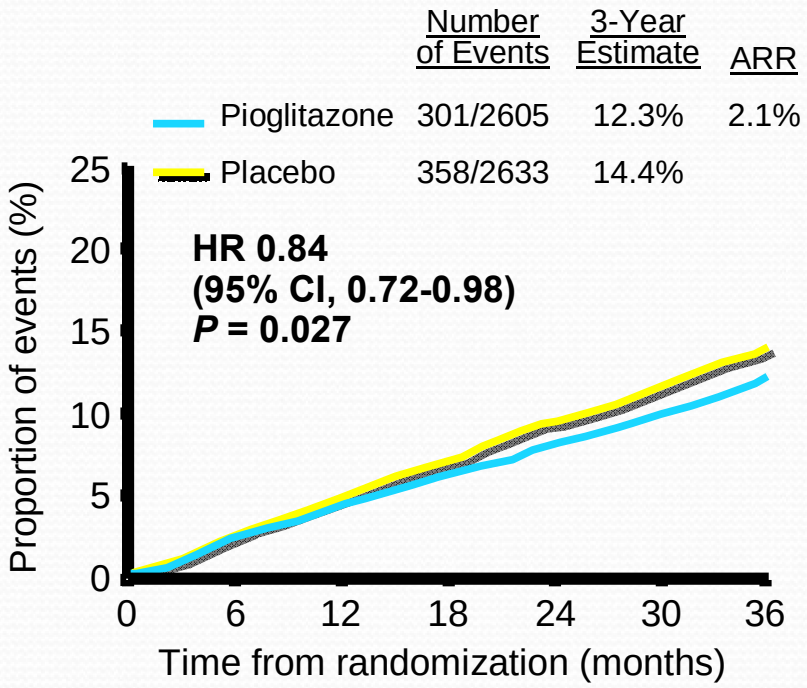
Nissen SE & Wolski K. *N Engl J Med* 2007; 356

PROactive: Reduction in Main Secondary End Point

1° composite end point: all-cause mortality, nonfatal MI (incl. silent MI), stroke, ACS, coronary or LE revasc., above-ankle amputation



Main 2° composite end point: all-cause mortality, nonfatal MI, and stroke



ARR: Absolute Risk Reduction
PROactive: Prospective Pioglitazone Clinical Trial in Macrovascular Events

Dormandy JA, et al. *Lancet.* 2005;366:1279-1289.

BARI-2D Results

Table 1. Kaplan-Meier Estimates for Event Rates at 5 Years*

	Death from Any Cause			*Major Cardiovascular Events*		
Variable	*Revascularization*	*Medical Therapy*	*p-value†*	*Revascularization*	*Medical Therapy*	*p-value†*
All patients						
Insulin sensitization, %	11.2	12.3	0.81	20.3	24.1	0.29
Insulin provision, %	12.2	12.0	0.85	25.2	24.1	0.63
p-value‡	0.75	0.90	0.78§	0.059	0.85	0.23§
PCI stratum						
Insulin sensitization, %	10.2	10.1	0.67	21.1	20.4	0.36
Insulin provision, %	11.4	10.3	0.56	24.9	21.7	0.28
p-value‡	0.79	0.94	0.92§	0.30	0.51	0.84§
CABG stratum¶						
Insulin sensitization, %	13.4	17.1	0.34	18.7	32.0	0.002
Insulin provision, %	13.9	15.6	0.67	26.0	29.0	0.58
p-value‡	0.83	0.71	0.72§	0.066	0.51	0.07§

N Engl J Med 360:2503, 2009

Diabetes Is More Than Just A Disease of Glucose Control!